

Tricuspid valve thrombus: A case report associated with gonadotropin-releasing hormone analogue therapy and review of the literature

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A 35-year-old woman with a previously repaired atrial septal defect was referred for preoperative evaluation before laparoscopic surgery. The patient was asymptomatic, and a transesophageal echocardiographic examination revealed a probable thrombus attached to the tricuspid valve. The patient's history included therapy with a gonadotropin-releasing hormone analogue and deep venous thrombosis five months earlier. The tricuspid valve thrombus disappeared after anticoagulant therapy. Warfarin was initiated for prophylaxis. During the follow-up, the patient was event-free during laparoscopic surgery and pregnancy (when warfarin was switched to acetylsalicylic acid) and gave birth to a healthy term baby. Because etiological investigations revealed no reason for the tricuspid valve thrombus, it was considered to be related to the procoagulant state induced by hormonal treatment. The patient was scheduled for close follow-up.

Key Words: Deep venous thrombosis; Gonadotropin-releasing hormone analogue; Oral contraceptive drugs; Pulmonary embolism; Tricuspid valve thrombus

Masses related to the tricuspid valve are infrequent pathologies of routine cardiology practice. Tumorous structures (especially fibroelastomas and carcinoid tumours) and vegetations due to right heart endocarditis are among the noted etiological factors. Isolated thrombi of the tricuspid valve are rare, and may yield confusion in differential diagnosis and therapy by mimicking vegetations or tumours.

CASE PRESENTATION

A 35-year-old woman with primary infertility undergoing a planned laparoscopic surgery was preoperatively evaluated because of a past atrial septal defect operation. She had atrial septal defect surgery 13 years previously and was asymptomatic at the time of writing. Gonadotropin-releasing hormone (GnRH) analogue therapy (leuproreotide acetate 11.25 mg in depot form; repeated every three months) had been initiated for endometriosis. Pain and swelling had occurred in her right leg after the first injection of the GnRH analogue six months earlier. Doppler ultrasonography revealed deep venous thrombosis (DVT). Low-molecular-weight heparin, acetylsalicylic acid and nonsteroidal anti-inflammatory drugs were prescribed, and elevation of the leg was advised. Prophylactic anticoagulant treatment was not continued. Her mother had a history of recurrent pulmonary embolism (PE) and nephrolithiasis. The patient's physical examination was normal except for a loud second heart sound. She was in sinus rhythm, and a right bundle branch block was present on her electrocardiogram. A chest x-ray was normal. The left heart chambers were normal, the

Thrombus valvulaire tricuspidien : Rapport de cas en lien avec un traitement par analogue de la gonadolibérine et survol de la littérature

Une femme de 35 ans ayant des antécédents de chirurgie pour correction d'une communication interauriculaire est adressée pour évaluation préopératoire en vue d'une chirurgie laparoscopique. La patiente était asymptomatique, mais l'examen échocardiographique transesophagien a révélé la présence d'un thrombus probable fixé à la valvule tricuspidienne. Les antécédents de la patiente incluaient un traitement par analogue de la gonadolibérine et une thrombose veineuse profonde, cinq mois auparavant. Le thrombus valvulaire tricuspidien est disparu après un traitement anticoagulant. La warfarine a été instaurée en prophylaxie. Au cours du suivi, la patiente n'a présenté aucune complication lors de sa chirurgie laparoscopique et de sa grossesse (lorsque la warfarine a été remplacée par de l'acide acétylsalicylique) et elle a donné naissance à un bébé à terme et en bonne santé. Comme les examens étiologiques n'ont pu donner d'explication à la présence du thrombus valvulaire tricuspidien, on l'a jugé en lien avec l'état procoagulant induit par le traitement hormonal. La patiente doit faire l'objet d'un suivi étroit.

right chambers were dilated and the atrial septum was intact on echocardiography. In addition, a sessile echogenic image (10 mm × 10 mm in size but not disturbing valvular movement) was detected on the atrial side of the tricuspid valve and was confirmed by transesophageal echocardiography (Figure 1). Because of the DVT history, the mass was initially interpreted to be a thrombus, and anticoagulant treatment was initiated (1000 U/h heparin infusion after an intravenous bolus of 5000 U; the dose was determined by the partial thromboplastin time). Because echocardiography revealed regression of the size of the mass on the third day (Figure 2), heparin infusion was switched to low-molecular-weight heparin (enoxaparin 0.6 mL subcutaneously twice per day). Meanwhile, the patient suffered from mild dyspnea, requiring ventilation. Perfusion scintigraphy for probable PE appeared normal. Doppler ultrasonography of the lower legs was also normal. Clinical and laboratory investigations for underlying connective tissue disorders were normal (sedimentation rate was normal, and antinuclear and anti-DNA antibodies were negative). Anticardiolipin antibodies (immunoglobulin [Ig]G, IgM and IgA) for antiphospholipid syndrome were also negative. Homocysteine, fibrinogen, protein C, protein S and von Willebrand factor levels were within normal ranges, and activated protein C resistance was not detected. Finally, the previous DVT attacks and the present tricuspid valve thrombus were attributed to treatment with the GnRH analogue. Because the effect of the drug's depot form lasts three months and the clinical events were encountered at the end of this period, they were

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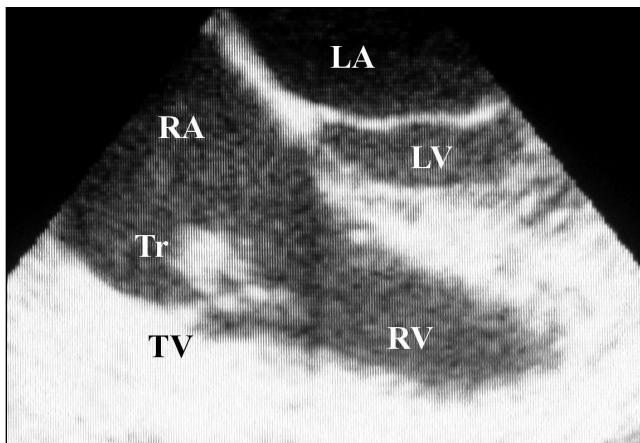


Figure 1) Transesophageal echocardiographic image displaying a sessile echogenic mass (thrombus [Tr]) attached to the atrial side of the tricuspid valve (TV). LA Left atrium; LV Left ventricle; RA Right atrium; RV Right ventricle

considered to be relatively long-lasting prothrombotic effects. A decision was made to anticoagulate the patient with warfarin according to prothrombin time monitoring. After one month, anticoagulant therapy was discontinued for the laparoscopic surgery. The pathological diagnosis was bilateral ovarian endometriosis. The patient was anticoagulated again postoperatively, and warfarin was switched to low dose acetylsalicylic acid (80 mg/day) after a follow-up at four months because of the planned pregnancy with in vitro fertilization. During the pregnancy, no cardiovascular problems were noticed, and the patient gave birth to a healthy term baby.

DISCUSSION

Although tricuspid valve thrombi are rare, they require special attention because they may mimic vegetations or tumorous masses. In many cases reported in the literature (1-5), the precise diagnosis was established after surgery. The only case diagnosed without surgical intervention was a patient with known antiphospholipid syndrome, for whom anticoagulant treatment was insufficient (4). Further anticoagulation in that case resolved the tricuspid and mitral valve thrombi. Although tricuspid valve involvement is not common, there have been several reported cases; thus, antiphospholipid syndrome should be suspected if a valvular or intracardiac thrombus is diagnosed in a patient without any organic heart disease (5,6). The laboratory markers for connective tissue diseases or antiphospholipid syndrome in our patient were all negative. In another reported case of organic heart disease (2), the thrombus was thought to have developed because of stagnant blood flow in the tricuspid valve pouch associated with a ventricular septal defect. In the case reported by Paolillo et al (1), a vascular structure associated with the right coronary artery was incidentally detected by coronary angiography and was diagnosed as an organized thrombus after surgical removal. Because DVT was detected in that patient, the tricuspid thrombus might have been a 'mass in transit' attached to the valve. The last reported case (3) was a woman undergoing oral progestin treatment who had no structural anomalies of the heart. The tricuspid valve thrombus in that case was reported to be associated with embolization from DVT or to have developed in situ. In situ tricuspid valve thrombus might have occurred because of blood stagnation in the right heart and minor endothelial valve injury from pulmonary hypertension. The case of the patient in the present paper is different from the former case because anticoagulant treatment resolved the thrombus and surgery was not required. However, it shares some common properties with the latter two cases because of the possible associations with DVT, particularly the effect of hormonal therapy (3). Because of this, we considered the possibility that

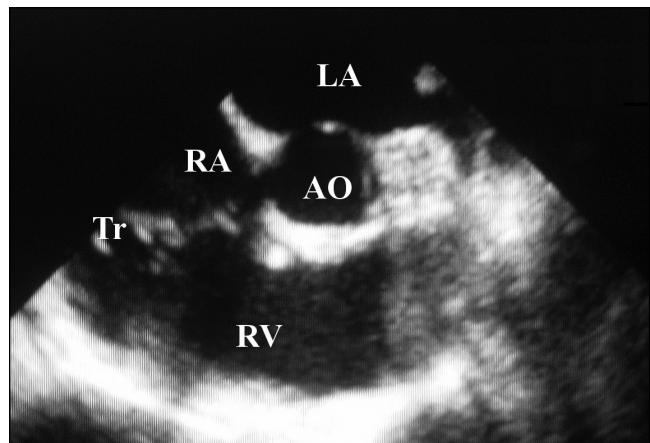


Figure 2) Control transesophageal echocardiographic image displaying regression of the size of the thrombus (Tr). AO Aorta; LA Left atrium; RA Right atrium; RV Right ventricle

the embolization was caused by DVT and the procoagulant effects of the hormonal treatment.

The incidences of DVT and PE in western communities are 1:1000 and 0.5:1000, respectively (7). There are hereditary (antithrombin deficiency, hyperhomocysteinemia, protein C and S deficiencies and factor V Leiden mutation) and acquired (advanced age, immobilization, venous insufficiency, varicose veins, pregnancy, oral contraceptive drugs, malignancies, congestive heart failure, central catheterization, systemic lupus erythematosus and antiphospholipid syndrome) factors in etiology (7). However, in almost one-half of cases, the underlying causal factor cannot be determined. In cases of DVT the most probable focus is the deep veins of lower extremities, but this cannot be proved in each case (8). The use of more sensitive diagnostic tools, such as magnetic resonance imaging, and performing ultrasonographic examinations as early as possible are very important (3). In some cases when a thrombus detaches from the focus and embolizes, echocardiography may reveal the right heart thrombus – the so-called 'mass in transit'. PE originating from a cardiac focus constitutes only a small number of cases, but can more likely be fatal because of massive embolism risk. In the International Cooperative Pulmonary Embolism Registry (9), the incidence of right heart thrombi was 4%. If a patent foramen ovale exists in addition to a right heart thrombus, these patients have a paradoxical embolism risk. Although there is no consensus on treatment with fibrinolytics, anticoagulants or surgical thromboembolectomy, emergent treatment is necessary, especially in cases with a mobile right heart thrombus.

In the present case, the patient's mother had suffered from recurrent PE attacks in her 30s and 40s, and had a parathyroidectomy after she was examined for recurrent renal colic attacks. A parathyroid adenoma was detected. Future malignancies may occur in 10% of idiopathic recurrent PE cases (7). Patients with idiopathic recurrent PE should be observed closely because of the malignancy risk. On the other hand, an echocardiographic study (10) revealed that in cancer patients, especially pancreatic and lung cancer patients, nonbacterial thrombotic vegetations in heart valves (frequently in mitral and aortic valves and rarely in tricuspid valves) can be detected. Investigations for underlying neoplasia were negative in the present case.

Oral contraceptive drugs increase the DVT risk by three to seven times. The risk is highest at the fourth month after initiation of therapy and disappears three months after discontinuation of the drug (10-12). In the reported case, a GnRH analogue was prescribed to suppress the gonadotropin axis and improve endometriosis symptoms. Although it is relatively infrequent with progestin-combined contraceptives,

DVT and thromboembolism can be seen with the use of hormonal therapies containing estrogen (12). The negative results of the search for any coagulopathic disorder in this patient, and the previous DVT attack occurring after the initiation of hormonal treatment suggest a similar relationship. When this kind of complication takes place, discontinuation of the therapy should be considered unless an obligatory indication for the drug use persists. In our opinion, the patient benefited from anticoagulant treatment during the DVT attack period, but lack of anticoagulant prophylaxis and repeated GnRH analogue injection resulted in the recurrence of the thrombotic process. The thrombus resolved with anticoagulant treatment and the patient did not suffer any complications, such as PE. The lack of recurrence or complications

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after treatment and during pelvic surgery and pregnancy (risk factors for DVT and PE) support our comment on the relationship between the GnRH analogue and the thrombotic events. The mild pulmonary hypertension and mild right heart dilation might have been due to residual findings of the operated ASD, or they might have been related to an undetermined pulmonary microembolism.

Consequently, hormonal therapies require close monitoring for pro-coagulant side effects and should be used cautiously in patients with PE history or DVT risk factors. If a tricuspid valve mass occurs during treatment with these drugs, unless any clinical instability or evidence of malignancy exists, short-term anticoagulation can be attempted before deciding on surgery.